REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

The Office Action Summary correctly indicates that claims 21-37 and 39-64 are pending in the application.

By the present amendment, Claims 21-37 and 38-43 have been canceled without prejudice or disclaimer of the subject matter disclosed therein.

By the present amendment, Claims 44, 48, 51, 56 and 62 have been amended.

Claim 44 has been amended to more clearly describe the claimed subject matter by correcting a grammatical error. Support for the amendments to claim 44 can be found throughout the specification, in the claims as originally filed and claim 44 as previously described.

Claim 48 has been amended to more clearly describe the claimed subject matter by deleting unnecessary recitations. Support for the amendments to claim 48 can be found in the specification and in at least the claims as filed and claim 48 as previously described.

Claim 51 has been amended to clarify its dependency to now depend from Claim 50, which in turn depends from Claim 44 from which it previously depended. Support for the amendment may be found in at least the claims as originally filed and claim 51 as previously presented.

Claim 56 has been amended to more clearly state the antecedent relationship of the claimed subject matter. Support for the amendment may be found at least in the claims as originally filed and claim 56 as previously described.

Claim 62 was amended to correct a typographical error to depend from claim 48 rather than 49. Support for the amendment may be found throughout the specification and at least in the claims as originally filed and claim 62 as previously described.

No reduction in the scope of Claims 44, 48, 51, 56, 62 and Claims which depend therefrom is believed to result from the foregoing amendments.

By the present amendment, new Claims 65-72 are added for examination.

Support for new Claim 65 can be found at least page 9, line 20 of the present specification.

Support for new claims 66 and 67 can be found at least page 16, line 30 of the specification.

Support for new claim 68 can be found at least in claim 27 as originally filed and page 13 line 6 of the present specification.

Support for new claims 69 to 72 can be found throughout the specification, in the claims as originally filed, and at least at page 27, lines 11-19 of the present specification.

No prohibited new matter is believed to have been introduced by way of the above Amendments. Furthermore, Applicants reserve the right to file a continuation or divisional application on subject matter canceled by way of the present Amendments.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 21-37 and 39-64 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled because the Examiner states that the specification does not enable any person skilled in the art to practice the invention commensurate in scope with the claims. Without acceding to the merits of the rejection, by the present amendment, Claims 21-37 and 39-43 have been canceled in order to expedite prosecution and to limit the number of issues on appeal, should an appeal become necessary. Applicants reserve the right to file a continuation or divisional application drawn to any subject matter canceled by the present amendment. The rejection is respectfully traversed with respect to Claims 44-64, and to the extent that the instant rejection might be applied to new claims 65-72, for the following reasons and for the reasons previously set forth in Paper No. 15.

The Official Action acknowledges that the specification is enabling for reducing tumor cell load in mice by administering a recombinant vector expressing E6 and E7 polypeptides of HPV-16 linked with a membrane anchoring sequence. The previous Official Action (Paper No. 13) acknowledged that the specification is enabling for

treatment of cancer or a tumor in a subject by subcutaneous, intraperitoneal, intramuscular, or scarification delivery of a vaccinia vector encoding the HPV E6 or E7 proteins. The previous Official Action (Paper No. 13) also acknowledged the enablement of prevention of cancer or a tumor in a mouse model. The Official Action alleges that the specification does not reasonably provide enablement for reducing tumor cell load in humans, or the use of any membrane anchoring sequence, or the use of any immunogenic polypeptide.

The Office has not met the burden required to make a *prima facie* rejection for lack or enablement. Moreover, it appears that the Examiner has misapplied the standard set forth in the M.P.E.P. The Examiner cites the M.P.E.P. at § 2164.01c which states "When a compound or composition is limited by a particular use, enablement of that claim should be evaluated based on that limitation. *See, In re Veack*, 947 F.2d 488, 495, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991)." The Examiner appears to suggest that not reciting a limitation to a particular use (e.g. reducing tumors in mice) means that every conceivable use of a claimed composition must be enabled by the specification under 35 U.S.C. § 112, first paragraph. Applicants assert that the cited portion of M.P.E.P. § 2164.01c means instead that only where a claim recites a limited use, should the enablement be evaluated for that limited use. The Examiner is directed to the following sentence of M.P.E.P. § 2164.01c which goes on to state, "In contrast, when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use." The present claims do not recite a limit one use. The present claims recite anitumoral compounds and methods of using such compounds. **Therefore any enabled use of the claimed compounds as antitumoral compounds precludes a rejection for lack of enablement.** The scope of the claims be considered is not the scope of conceivable uses.

The presently claimed invention is drawn to embodiments directed to a vector-based antitumoral composition expressing E6 and/or E7 polypeptide of a papillomavirus linked to a membrane anchoring sequence. Accordingly, Applicants submit that presently claimed invention is clearly well within the scope of the enablement acknowledged in the Official

Action. Neither the present Official Action nor the previous Official Action has presented reason to doubt that the full range the compounds embraced by the present claims are not enabled for use as antitumoral compounds and methods.

The Board of Patent Appeals and Interferences and the Federal Circuit have made it clear that there must be substantive reason to doubt that the specification is insufficient before the burden shifts to the applicant. The case law on point is worth repeating. Only when "the examiner's basis for questioning the sufficiency of the disclosure is reasonable the burden shifts to appellants to come forward with evidence to rebut this challenge." *Ex parte Dash*, 27 USPQ2d 1481, 1484 (Bd. Pat. App. and Int. 1993). "When rejecting a claim under the enablement requirement of section 112, the PTO bears the initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. If the PTO meets this burden, the burden then shifts to the applicant to provide suitable proofs indicating that the specification is indeed enabling." *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)(with emphasis).

The Examiner has not presented substantive reasons to doubt that the presently claimed invention may be used as disclosed with any appropriate cell surface membrane anchoring sequence recognized in the art, or that improved efficacy could not be achieved with a vector encoding any immunogenic polypeptide derived from a polypeptide encoded by the E6 or E7 early region of a papillomavirus genome modified to have a membrane location at the surface of the cells in which it is expressed.

To the contrary, the specification demonstrates the enablement of the invention in several working examples. The subject application demonstrates regression of papillomavirus-induced tumors following administration of a vector which directs the expression of cell-surface anchored E6 and/or E7 HPV polypeptide(s), alternatively in combination with an immunostimulant. Such tumor protective effect has been shown for

three different tumor models (BMK-16 myc cells in Example 3, E7W1 cells in Example 6 and TC-1 cells in Examples 8 and 9). In all cases, recombinant vectors producing membrane associated papillomavirus early antigens are more efficient than recombinant vectors producing native forms of the same antigens. Moreover various routes of administration and dosages have been explored, all confirming the superiority of the cell-surface anchored antigens. In the TC1 tumor grafted mouse model, protection achieves in certain conditions 100% both in therapeutical (Example 9 of the present application) and prophylactical (Example 8) conditions.

The enablement of the invention demonstrated in the specification is confirmed in clinical trials. The experimental data collected from preclinical studies were assessed sufficiently successful to justify further clinical development. In this respect, we direct the Examiner's attention to the attached press releases reporting that phase II clinical trials have been initiated at the beginning of this year, to evaluate the claimed invention for use against cervical cancers and vulvar epithelial neoplasia. (Attached as Exhibit 1.) The Bioworld article states that the product (recombinant MVA expressing membrane-associated E6 and E7 HPV polypeptides and IL-2) has undergone Phase I clinical trials both in the USA and in Europe on patients with various stages of cervical lesions. (Etheridge, *BioWorld International*, January 2, 2002, American health Consultants.) These trials have demonstrated safety and tolerability of the vaccine, and provided evidence of an immune response in some patients.

The enablement demonstrated in the specification is sufficient under the law. It has never been the law that a product or process must be developed to the extent that usefulness in humans is established before a patent is granted. The Examiner is respectfully reminded that the Federal Circuit has cautioned the PTO not to "confuse[] the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *In re Brana*, 34 USPQ2d 1437, 1442 (Fed. Cir. 1995). The Federal Circuit also stressed that precedential authority "has determined that proof of an alleged pharmaceutical property for

a compound by statistically significant tests with standard experimental animals is sufficient to establish utility." *Id.* "FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were [the PTO] to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer." *Id.* at 1442-43. Thus, it is sufficient to show that a therapeutic or prophylactic immune response may be achieved in an appropriate animal model. None of the references cited in the record have shown that the model systems used are not art accepted models now as they were at the time of the application.

Concerning more specifically the TC1 tumor model from which most of the experimental data disclosed in the present application are obtained, the Examiner's attention is invited to Lin et al. (1996, *Cancer Res.*, 56:21-26, attached as Exhibit 2), describing the TC1 cell line. In this respect, primary lung epithelial cells from C57BL/6 mice were immortalized by HPV-16 E6 and E7 and activated ras oncogen. As stated at the top of page 22, "this cell line mimics the natural sequence of tumor progression of cervical cancer in which HPV-16 E6 and E7 immortalize cells and transform the cells into advanced tumor cells with metastatic potential. This cell line thus provides an excellent model ..."). It should be stressed that the HPV-transformed TC1 cell line has been widely used by the major scientific teams in the HPV field to evaluate the antitumor effect of various therapeutic molecules against HPV-16-induced tumors, as reflected by the following publications :

- Wai Yan Lui et al. (2002, *Human Gene Therapy*, 13:177-185) for testing IL-12- encoding naked DNA (attached as Exhibit 3) ;

- Daemen et al. (2002, *Gene Ther.*, 9:85-94) for testing alpha virus vector expressing E6 and E7 fusion protein (attached as Exhibit 4);
- Greenstone et al. (1998, *PNAS*, 95:1800-1805) for testing chimeric papillomavirus-like particles (attached as Exhibit 5); and
- Ji et al. (1999, *Human Gene Therapy*, 10:2727-2740) for testing a DNA construct expressing the E7 polypeptide linked to an endosomal/lysosomal targeting signal (attached as Exhibit 6).

The foregoing is further support of the fact that the experimental evidence provided in the present application have been obtained in an art recognized animal model. This constitutes sufficient evidence that those skilled in this art would not have doubted the assertions of utility set forth in the specification.

From a practical point of view, moreover, it is virtually impossible to ascertain utility in humans before filing a patent application. Indeed, human trials require special permission from national regulatory bodies before starting experimentation on human beings. Such permissions are not lightly given and may take years to be obtained. Importantly, the present invention was considered sufficiently successful and useful by French and Mexican regulatory authorities to grant permission to proceed with additional human trials against cervical cancers and vulvar epithelial neoplasia.

Further, when human trials are begun, the first human candidates are those with advanced cancers who have relapsed after conventional therapies, so that a complete cure or therapeutic utility is virtually impossible to demonstrate. Moreover, they receive low dose of the product to be evaluated. It has also to be remembered that phase I trials are designed to establish safety rather than effectiveness of the product. Accordingly, it would be deleterious to any applicant to delay filing a patent application until "therapeutic effectiveness" in humans is conclusively because any publications authored by the inventors or others having knowledge of the inventor's work would destroy novelty.

Morever, the references cited in the Official Action do not demonstrate a reason to doubt the enablement of the claimed invention. The Examiner asserts that

extrapolation of applicant's animal models to potential human therapy is questionable based on Bodey et al. (2000, Anticancer Res. 20, 2665-3676) which review cancer immunotherapy vaccines and Radoja et al. (2000, Mol. Med. 6, 465-479) which discuss the status of immunity in cancer patients. According to the Examiner, although the instant specification provides *ex vivo* and *in vivo* data in a mouse tumor model to illustrate the enabled therapeutic uses of the claimed invention, it is not enabled for its full scope (e.g. treatment of human cancers) because of the art-recognized barriers in achieving successful cancer immunotherapy and differences in immune responses between a mouse tumor model and cancer patients.

Bodey et al. addressed many different approaches in cancer immunotherapy which have been devised to induce immune activation against the tumoral cells. The approaches reviewed by Bodey et al. are mainly based on :

- tumor-associated antigens (TAAs) which are self antigens (e.g. oncofetal antigens, growth factors receptors, oncogene, tumor suppressor gene products, cell-surface carbohydrate, among others).
- Whole cell-derived vaccines ;
- Anti-idiotypic monoclonal antibodies ;
- Administration of cytokines ;
- Dendritic cell vaccines

The quotations from Bodey et al. cited in the Official Action do not reflect the broader context of the review. Bodey et al., in fact, report numerous positive trials in cancer patients treated by immunotherapy. For example, the complex carbohydrate molecule GloboH conjugated with QS-21 adjuvant was administered to patients with prostate cancer who have relapsed after primary therapies. The vaccine, given as five subcutaneous injections over 26 weeks has been shown to be safe and capable of inducing specific high titer IgM antibodies against goboH. Its immunogenecity was confirmed in prostate cancer patients with a broad range of stage and tumor burdens (end of 4th paragraph page 2667, first column). Concerning MUC-1 based immunotherapy, cellular

and humoral immune responses have been recorded in patients with advanced malignancy (first paragraph, page 2667, second column). Concerning active specific immunotherapy, the principle has been established that stimulation of the immune response by "crude" vaccines led in a significant number of patients to rejection of tumor masses, in some instance for 10 years or more. The bonafide examples of tumor regression observed with whole tumor cell vaccines give support for the belief that active specific immunization can induce a therapeutically effective immune response in melanoma patients (second paragraph page 2668, second column). Concerning the anti-idiotypic approach, treatment with Ab3 antibodies results in a patient in a complete clinical response, with resolution of soft tissue disease, and 6 patients had stable disease, ranging from 9 to 23 months (second paragraph page 2669, second column). 49% of patients with non-Hodgkin's B-cell lymphoma treated with a tumor Ig protein generated specific immune responses against the idiotypes of their tumor Ig. Two patients who had residual disease experienced complete tumor regression in association with the development of these immune responses. The median duration of freedom from disease progression and overall survival of all 20 patients mounting an anti-idiotype immune response are significantly prolonged (end of page 2669, second column).

Applicants respectfully direct the Examiner's attention to the fact that the statement by Bodey et al. in the last section discuss the failure of specific cancer vaccines to produce enhancement of immunity in cancer patients although immune responses were observed in animal models is clearly directed to peptide vaccines based on self TAAs antigens and cytokine-expressing tumor cells. Further, Bodey et al. recognize that the observed immunotherapy failure can also be explained by the fact that most clinical trials are conducted in advanced terminal cases, after all traditional modalities have been exhausted. As mentioned page 2674, the use of such vaccines to stimulate the host's immune system may be in vain if the particular TAAs represented in the vaccine preparation are no longer present on the most advanced subsets of cancer cells.

In contrast to the failed antigens referred to by Bodey et al. in the cited quotation, the present invention targets non-self antigens (E6 and/or E7 papillomavirus polypeptides)

that have been reported to be continuously expressed during tumor development. Indeed, as indicated in Boursnell et al. (1986, *Vaccine,* 14:1485-1494 ; cited in previous office Action), "a consistent feature of cervical tumor cells is the retention and expression of the portion of the virus genome encoding two early virus proteins, E6 and E7... Furthermore, recent studies have suggested that continued expression of E6 and E7 within tumor cells is required to maintain the transformed state." (see page 1485, first paragraph, second column). Therefore, the present invention does not share the deficiency reported in Bodey et al. since the particular immunogenic polypeptides comprised in the composition of the present invention are required for maintenance of the malignant phenotype. In addition, the membrane associated status of these antigens represents optimal presentation of these tumor antigens to the host's immune system for activation of a CTL response.

Therefore, Applicants believe that the preclinical evidence disclosed within the subject application provide a reasonable enablement without the requirement of undue experimentation. Experimentation may be significant where such experimentation is routine, it should not be considered undue.

For at least the foregoing reasons, and those presented in Paper No. 15, we believe that the scope of the invention embraced by the present claims is well within the enablement provided by the specification; and, therfore, request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claim Rejections under 35 USC § 112, second paragraph

Claims 21-37, and 39-64 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Claims 21- 37 and 39-43 have been canceled. The rejection is respectfully traversed with respect to the remaining claims.

Claim 44 is alleged to be vague for the recitation of "modified by inserting a membrane anchoring sequence" The Examiner considers that it is unclear as to which part of the polypeptide, the membrane targeting sequence is inserted and whether such insertion would cause a change of immunogenicity.

Applicants submit that one skilled in the art would reasonably understand in which part of the polypeptide to insert the membrane-anchoring sequence in accordance with the guidance provided in the specification and the general knowledge in the art. The linkage to the membrane-anchoring sequence does not modify the immunogenicity of the papillomavirus as such but it provides an optimal presentation to the host's immune system as mentioned page 3 lines 27-34 of the present application.

Claim 44 is also alleged to be vague because the term membrane encompasses cellular and intracellular membranes. Applicants assert that the amendments introduced in response to the previous Office Action made clear that the term "membrane" as used in Claim 44 refers to the cellular membrane since it is recited that the membrane location is at the surface of the cells.

For at least the forgoing reasons, Applicants submit that one of skill in the art will be aware of the metes and bounds of the presently claimed invention. Accordingly, withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Rejections under 35 U.S.C. § 102

Claims 21-23, 35-37 and 41 have been rejected under 35 USC 102(b) as allegedly being anticipated by Arnold et al. (1994, Virol. 198, 703-708). Moreover, claims 21 and 36 have been rejected under 35 USC 102(b) as allegedly being anticipated by Geogiou et al. (US Patent 5,348,867) and under 35 USC 102(e) as allegedly being anticipated by Stahl et al. (US Patent 5,958, 736).

Without acceding to the merits of the rejections, but simply in order to expedite prosecution, Claims 21-37, and 39- 43 have been canceled without prejudice or disclaimer. Therefore, these rejections have been rendered moot. Accordingly, withdrawal of the rejections under 35 U.S.C. § 102 is respectfully requested. Applicants thank the Examiner for the withdrawal of previous rejections under 35 U.S.C. §§ 102 and 103.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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Attachment to Amendment dated June 17, 2002

Marked-up Claims 44, 48, 51, 56 and 62

44. (Amended) An antitumoral composition comprising at least one recombinant vector comprising sequence encoding at least one immunogenic polypeptide, wherein said polypeptide is a polypeptide naturally having a nonmembrane location and which is modified by inserting a membrane anchoring sequence so as to have a membrane location at the surface of the cells in which it is expressed, wherein said vector is a non-integrative vector and wherein said immunogenic polypeptide is derived from a polypeptide encoded by the E6 or E7 early [regions] region of a papillomavirus genome.

48. (Amended) The antitumoral composition according to claim 44, wherein [at least one immunogenic polypeptide is derived from an early E6 or E7 polypeptide and] said vector further comprises a sequence encoding at least one [immunogenic] polypeptide [is] derived from a late polypeptide of a papillomavirus.

51. (Amended) The antitumoral composition according to claim [45] 50, wherein said compound enhancing the antitumoral effect is an immunostimulator.

56. (Amended) A recombinant vector comprising the sequences encoding one or more immunogenic polypeptide(s), wherein at least one of said polypeptides is a polypeptide [of] as defined in claim 44.

Attachment to Amendment dated June 17, 2002

Marked-up Claims 44, 48, 51, 56 and 62

62. (Amended) The antitumoral composition according to claim [49] 48, wherein at least one immunogenic polypeptide is such that:

(1) said immunogenic polypeptide has a sequence homologous or identical to that shown in SEQ ID NO: 1 and wherein said recombinant vector further comprises sequence encoding the L1 protein of a papillomavirus and/or the L2 protein of a papillomavirus,

(2) said immunogenic polypeptide has a sequence homologous or identical to that shown in SEQ ID NO: 2, and wherein said recombinant vector further comprises sequence encoding the L1 protein of a papillomavirus and/or the L2 protein of a papillomavirus, or

(3) said immunogenic polypeptide has a sequence homologous or identical to that shown in SEQ ID NO: 1, an immunogenic polypeptide having a sequence homologous or identical to that shown in SEQ ID NO: 2, and wherein said recombinant vector further comprises sequence encoding the L1 protein of a papillomavirus and/or the L2 protein of a papillomavirus.